Tetrahedron Letters 52 (2011) 5133–5135

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An improved stereoselective total synthesis of (*R*)-rugulactone

Abhishek Goswami, Partha Pratim Saikia, Bishwajit Saikia, Devdutt Chaturvedi, Nabin C. Barua *

Natural Products Chemistry Division, North East Institute of Science & Technology (CSIR), Jorhat 785006, Assam, India

ARTICLE INFO

Article history:
Received 8 June 2011
Revised 22 July 2011
Accepted 23 July 2011
Available online 29 July 2011

Keywords:
Rugulactone
α-Pyranon-2-one
NF-κB inhibitor
Julia-Kocienski olefination

ABSTRACT

A novel route for the stereoselective total synthesis of (*R*)-rugulactone **1** has been developed, starting from substituted epoxide **4** and 3-phenylpropionaldehyde **5** employing Julia-Kocienski olefination as a key step to construct *E*-configured α,β-unsaturated keto-group. The overall yield of the synthesized rugulactone is 19.94% and is better than the reported methods.

The natural products bearing 5,6-dihydro-α-pyrone skeleton having substituted alkyl side chain at the C-6 position have attracted much attention since the last decade due to their medicinal potential due to the *Michael* acceptor property of α,β-unsaturated α-pyrones for the amino acid residues of the receptors.[1] Due to the Michael acceptor property of this class of molecules they have displayed diverse arrays of potential biological activities, such as antitumor, anti-inflammatory, antibacterial, antiviral, antifungal, antialzheimer, antidiabetic, antioxidant, etc.[2] The arylalkyl-substituted α,β-unsaturated δ-lactones are omnipresent metabolites of the evergreen trees of the genus *Cryptocarya* which are well known for their potential medicinal properties.[3] Recently, 6-arylalkyl-5, 6-dihydro-*2H*-pyran-2-one, (*R*)-rugulactone **1** was isolated from the dichloromethane extract of *Cryptocarya rugulosa*, which was found to inhibit nuclear factor-κB (NF-kB) activation pathway and is active against many types of cancer, exhibiting up to fivefold induction of IκB at 25 μg/mL in human lymphoma cell lines.[4] In view of the potential biological activities displayed by this molecule, several researchers have put their efforts toward the synthesis of rugulactone involving novel strategies.

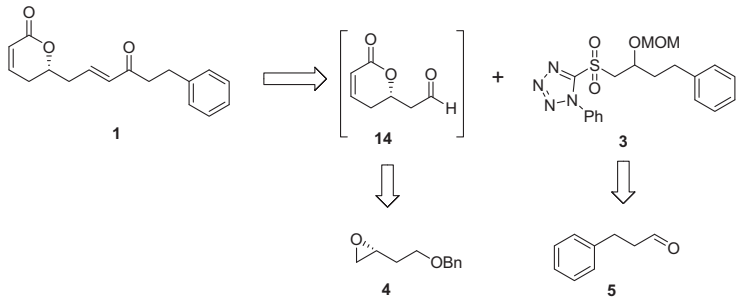
To the best of our knowledge, six syntheses of rugulactone have already been explored in recent years.[5] The first total synthesis reported by Mohapatra et al. involves the ring closing metathesis reaction and Horner–Wadsworth–Emmons reaction as key steps.[5a] The second synthesis of Venkateswarlu et al. employed Keck's asymmetric allylation and Grubb's cross metathesis reaction as key steps,[5b] whereas the third synthesis reported by Fadnavis's group involved a chemoenzymatic pathway employing *Candida rugosa* lipase.[5c] The other three syntheses involved mainly the ring closing metathesis reaction employing diversity of the key intermediates.[5d,e] Majority of the reported synthetic routes have several limitations, such as the use of costly reagents, multiple synthetic steps, and overall low yields of the desired product. Consequently, there is continued interest in developing new and efficient synthetic routes for the synthesis of rugulactone. Our group has been working since the last several years on the synthesis of structurally diverse biologically active natural products employing novel and efficient synthetic routes.[6] In this communication, we wish to report a new and efficient total synthesis of (*R*)-rugulactone **1** starting from substituted epoxide **4** and 3-phenylpropionaldehyde **5** employing Julia-Kocienski olefination and Yamaguchi epoxide opening as key steps.[10]

Our retrosynthetic plan for the synthesis of target compound **1** is depicted in Scheme 1. We proposed that the synthesis of (*R*)-rugulactone **1** could be achieved through the Julia-Kocienski olefination between aldehyde **14** and sulfone **3** to construct the C_8–C_9 *trans* double bond. Aldehyde **14** could be synthesized starting from the epoxide **4**. The synthesis of the sulfone derivative **3** could be achieved from commercially available 3-phenyl propionaldehyde **5**. It has been postulated that the stereochemistry at C-6 position could be secured by the regioselective ring opening of epoxide **4**.

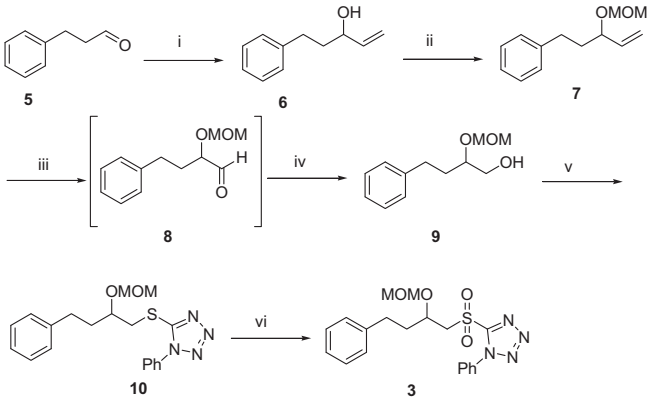
To achieve the synthesis of target compound **1**, 3-phenyl propionaldehyde **5** was treated with vinylmagnesiumbromide in THF at −30 °C to afford the allyl alcohol **6** in 90% yield (Scheme 2). Allyl alcohol **6** was then protected as the MOM ether to furnish compound **7**. Oxidative cleavage of **7** with OsO_4/$NaIO_4$ in dioxane/H_2O gave aldehyde **8**, which without further purification was reduced with sodium borohydride in methanol to afford the primary alcohol **9**. Alcohol **9** was converted into sulfide **10** by a Mitsunobu reaction employing 1-phenyl-1*H*-tetrazole-5-thiol

* Corresponding author. Tel.: +91 376 2371283; fax: +91 376 2370011.
E-mail addresses: ncbarua2000@yahoo.co.in, ncbarua12@rediffmail.com (N.C. Barua).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.109



Scheme 1. Retrosynthetic analysis of (*R*)-rugulactone **1**.



Scheme 2. Reagents and conditions: (i) vinyl magnesium bromide, THF, −30 °C, 90%; (ii) MOMCl, DIPEA, 0 °C to rt, 90%; (iii) OsO_4, 2,6-lutidine, $NaIO_4$, dioxane/water (3:1); (iv) $NaBH_4$, MeOH, 0 °C, 95% over two steps; (v) TPP, PTSH, DIAD, THF, 0 °C to rt, 85%; (vi) *m*-CPBA, CH_2Cl_2 0 °C, 90%.

(PT-SH) as the nucleophile in 85% yield. Sulfide **10** was then oxidized with *m*-CPBA to yield the corresponding sulfone **3**.

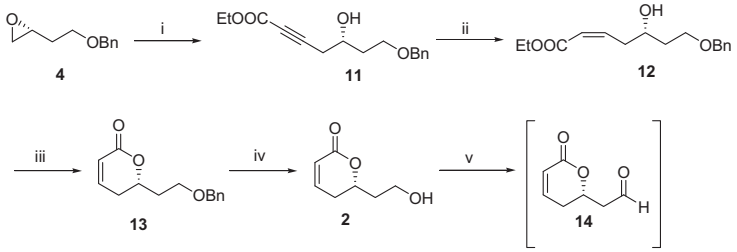
To achieve the synthesis of α-pyrone subunit **2**, the known epoxide[7] **4** was coupled with ethyl propionate under Yamaguchi coupling condition[8] affording the corresponding propargylic alcohol **11** in 93% yield (Scheme 3). Subsequent hydrogenation of compound **11** over Lindlar catalyst furnished unsaturated ester **12**. Hydrolysis of the ester group of compound **12** proceeded with in situ lactonization to deliver lactone **13**. Removal of the benzyl protecting group of compound **13** with DDQ in dichloromethane/water furnished the α-pyrone subunit **2**. Aldehyde **14** was prepared by oxidation of **2** using Dess–Martin periodinane and was used without further purification.

After achieving the synthesis of both the fragments (compounds **14** and **3**), we then proceeded to the Julia-Kocienski[9] olefination (Scheme 4). Utilizing the robust and reliable procedure reported by Kocienski, sulfone **3** was deprotonated with potassium bis(trimethylsilyl)amide (KHMDS) and subsequently treated with crude aldehyde **14** to afford compound **15** in 65% yield. MOM deprotection of **15** and subsequent oxidation of the resulting crude alcohol with IBX furnished the target molecule **1** in 92% yield. The physical and spectral properties of our synthetic target compound **1** closely matched with the literature data.

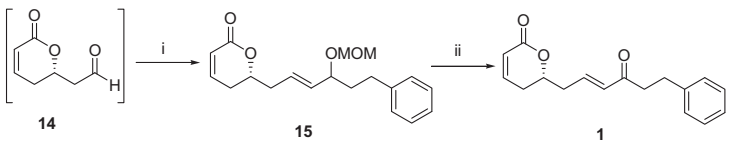
In conclusion, a convergent synthesis of (*R*)-rugulactone **1** has been achieved starting from commercially available inexpensive 3-phenyl-1-propanal **5** and the known epoxide **4** employing Yamaguchi coupling and Julia-Kocienski olefination reaction as key steps with the overall yield of 19.94%.

Acknowledgments

We are grateful to the Director, NEIST, Jorhat, for providing facilities to carry out this work. A.G. thanks UGC, and P.P.S. and B.S. thanks CSIR, New Delhi for research fellowships.



Scheme 3. Reagents and conditions: (i) Ethyl propionate, *n*-BuLi, $BF_3.OEt_2$, −78 °C, THF, 93%; (ii) H_2, Lindlar catalyst, quinoline, EtOAc, 91%; (iii) 3% HCl in methanol, 90%; (iv) DDQ, CH_2Cl_2–H_20, 80%; (v) DMP, dry CH_2Cl_2, 0 °C to rt.



Scheme 4. Reagents and conditions: (i) **3**, KHMDS, dry THF, −78 °C, 65%; (ii) (a) 37% HCl, ethanol, 40 °C, 93%; (b) IBX, dry DMSO, 92%.

References and notes

1. Buck, S. B.; Hardouin, C.; Ichikawa, S.; Soenen, D. R.; Gauss, C. M.; Hwang, I.; Swinkle, M. R.; Bonness, K. M.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 15695–15696.
2. Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040.
3. Marco, J. A.; Carda, M.; Murga, J.; Falomir, E. *Tetrahedron* **2007**, *63*, 2929–2958.
4. Meragelman, T. L.; Scudiero, D. A.; Davis, R. E.; Staudt, L. M.; McCloud, T. G.; Cardellina, J. H., II; Shoemaker, R. H. *J. Nat. Prod.* **2009**, *72*, 336–339.
5. (a) Mohapatra, D. K.; Das, P. P.; Reddy, D. S.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 5841–5944; (b) Reddy, D. K.; Shekhar, V.; Reddy, T. S.; Reddy, S. P.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2009**, *20*, 2315–2319; (c) Reddipalli, G.; Venkataiah, M.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2010**, *21*, 320–324; (d) Cros, F.; Pelotier, B.; Piva, O. *Eur. J. Org. Chem.* **2010**, 5063–5070; (e) Reddy, D. K.; Shekhar, V.; Prabhakar, P.; Babu, B. C.; Siddhardha, B.; Murthy, U. S. N.; Venkateswarlu, Y. *Eur. J. Med. Chem.* **2010**, *45*, 4657–4663; (f) Allais, F.; Aouhansou, M.; Majira, A.; Ducrot, P.-H. *Synthesis* **2010**, *16*, 2787–2793; (g) Bose, D.; Fernandez, E.; Pietruszka, J. *J. Org. Chem.* **2011**, *76*, 3463–3469.
6. (a) Saikia, P. P.; Baishya, G.; Goswami, A.; Barua, N. C. *Tetrahedron Lett.* **2008**, *49*, 6508–6511; (b) Saikia, P. P.; Goswami, A.; Baishya, G.; Barua, N. C. *Tetrahedron Lett.* **2009**, *50*, 1328–1330; (c) Boruwa, J.; Barua, N. C. *Tetrahedron* **2006**, *62*, 1193–1198; (d) Gogoi, N.; Boruwa, J.; Barua, N. C. *Eur. J. Org. Chem.* **2006**, 1722–1725; (e) Boruwa, J.; Gogoi, N.; Barua, N. C. *Org. Biomol. Chem.* **2006**, *4*, 3521–3525.
7. Trost, B. M.; Amans, D.; Seganish, W. M.; Chung, C. K. *J. Am. Chem. Soc.* **2009**, *131*, 17087–17089.
8. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.
9. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.
10. *Selected analytical data for unknown compounds: (3-Methoxymethoxy-pent-4-enyl)-benzene* (**7**): IR ($CHCl_3$) ν = 3063, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5H), 5.77–5.66 (m, 1H), 5.25 (dd, J = 0.7, 5.4 Hz, 2H), 4.74 (d, J = 6.9 Hz, 1H), 4.57 (d, J = 6.7 Hz, 1H), 4.04–4.02 (m, 1H), 3.39 (s, 3H), 2.76–2.65 (m, 2H), 1.96–1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.0, 138.2, 128.7, 128.4, 125.8, 117.4, 93.9, 55.5, 37.2, 31.7. MS (ESI): m/z = 206.5 (M^+).
2-Methoxymethoxy-4-phenylbutan-1-ol (**9**): IR ($CHCl_3$) ν = 3427, 3060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 4.78 (d, J = 6.9, 1H), 4.67 (d, J = 6.9 Hz, 1H), 3.58–3.51 (m, 3H), 3.44 (s, 3H), 3.25 (br s, 1H), 2.76–2.64 (m, 2H), 1.85–1.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.7, 128.4, 128.3, 126.2, 125.9, 97.0, 81.5, 65.6, 55.7, 33.3, 31.7. MS (ESI): m/z = 210.8 (M^+).
5-(2-Methoxymethoxy-4-phenylbutylsulphanyl)-1-phenyl-1H-tetrazole (**10**): IR ($CHCl_3$) ν = 3060, 2927 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58–7.52 (m, 5H), 7.30–7.16 (m, 5H), 4.76 (d, J = 6.9 Hz, 1H), 4.69 (d, J = 7.0 Hz, 1H), 4.01–3.97 (m, 1H), 3.76 (dd, J = 4.7, 13.4 Hz, 1H), 3.63 (dd, J = 5.7, 13.4 Hz, 1H), 3.38 (s, 3H), 2.78–2.70 (m, 2H), 2.01–1.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.4, 141.4, 133.6, 130.2, 129.8, 128.5, 128.3, 126.0, 123.8, 96.1, 75.4, 56.0, 37.9, 35.7, 31.4; MS (ESI): m/z = 371.7 (M^+).
5-(2-Methoxymethoxy-4-phenylbutan-1-sulfonyl)-1-phenyl-1H-tetrazole (**3**): IR ($CHCl_3$) ν = 3061, 2931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.59 (m, 5H), 7.31–7.15 (m, 5H), 4.68 (d, J = 6.9 Hz, 1H), 4.55 (d, J = 7.0 Hz, 1H), 4.34–4.26 (m, 1H), 4.03 (dd, J = 7.2, 14.8 Hz, 1H), 3.88 (dd, J = 4.4, 14.9 Hz, 1H), 3.35 (s, 3H), 2.72 (m, 2H), 2.08–2.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.1, 140.7, 132.9, 131.6, 129.7, 128.6, 128.3, 126.2, 125.4, 96.5, 76.7, 71.9, 60.1, 56.2, 36.2, 30.7; MS (ESI): m/z = 425.13 (M^++Na).
(5S)-7-Benzyloxy-5-hydroxy-hept-2-ynoic acid ethyl ester (**11**): $[\alpha]_D^{20}$ = +1.17 (C 1.0, $CHCl_3$). IR ($CHCl_3$): 3399, 2235, 1708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H), 4.52 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 4.06 (m, 1H), 3.77–3.65 (m, 2H), 3.37 (br s, 1H), 2.56–2.52 (m, 2H), 1.92–1.85 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.6, 137.6, 128.5, 128.4, 127.9, 85.6, 74.6, 73.4, 69.3, 69.1, 61.9, 35.3, 27.2, 14.0; MS (ESI): m/z = 276.1 (M^+).
(5S, Z)-7-Benzyloxy-5-hydroxyhept-2-enoic acid ethyl ester (**12**): $[\alpha]_D^{20}$ = −10.5 (C 0.85, $CHCl_3$); IR ($CHCl_3$) ν: 3422, 1716, and 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.3 (m, 5H), 6.41–6.35 (m, 1H), 5.92 (dd, J = 3, 15 Hz, 1H), 4.52 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.01 (m, 1H), 3.74–3.65 (m, 2H), 3.28 (br s, 1H), 2.87–2.81 (m, 2H), 1.82–1.77 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 146.2, 137.8, 128.4, 127.7, 121.4, 67.9, 66.7, 60.0, 36.5, 36.3, 14.2; MS (ESI): m/z = 278.4 (M^+).
(6S, Z)-6-(2-Benzyloxyethyl)-5, 6-dihydro-pyran-2-one (**13**): $[\alpha]_D^{20}$ = −42.9 (C 1.3, $CHCl_3$); IR ($CHCl_3$) ν: 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.32 (m, 5H), 6.91–6.85 (m, 1H), 6.05 (dd, J = 1.6, 9.7 Hz, 1H), 4.67–4.63 (m, 1H), 4.56 (d, J = 5.31 Hz, 2H), 3.71–3.62 (m, 2H), 2.39–2.35 (m, 2H), 2.07–1.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.4, 145.2, 138.1, 128.4, 127.7, 121.3, 75.2, 73.3, 65.6, 35.1, 29.5; MS (ESI): m/z = 232.7 (M^+).
(6S, Z)-6-(2-Hydroxyethyl)-5, 6-dihydro-pyran-2-one (**2**): $[\alpha]_D^{20}$ = −116.0 (C 1.25, $CHCl_3$); IR ($CHCl_3$) ν = 3399, 1701, 1622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.95–6.88 (m, 1H), 6.06 (dd, J = 1.7, 9.7 Hz, 1H), 4.70–4.65 (m, 1H), 3.92–3.82 (m, 2H), 2.43–2.38 (m, 2H), 2.05–1.91 (m, 2H), 1.88 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.6, 145.6, 121.1, 75.6, 58.2, 37.3, 29.5; MS (ESI): m/z = 142.3 (M^+).
(6R)-6-(4-Methoxymethoxy-6-phenyl-hex-2-enyl)-5,6-dihydro-pyran-pyran-2-one (**15**): $[\alpha]_D^{20}$ = +2.5 (C 0.6, $CHCl_3$); IR ($CHCl_3$): ν = 1735, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82–7.79 (m, 1H), 7.59 (dd, J = 7.5, 25.5 Hz, 1H), 7.30–7.18 (m, 5H), 5.75–5.66 (m, 1H), 5.25 (d, J = 14 Hz, 1H), 5.20 (m, 1H), 4.74 (d, J = 6.6 Hz, 1H), 4.57 (d, J = 6.7 Hz, 1H), 4.05–4.02 (m, 1H), 3.39 (s, 3H), 2.76–2.65 (m, 2H), 1.96–1.82 (m, 2H), 1.64 (m, 2H), 1.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.0, 138.1, 137.5, 132.4, 130.0, 128.3, 128.2, 125.8, 117.4, 93.8, 55.5, 37.1, 31.7, 29.7; MS (ESI): m/z = 316.1 (M^+).
(6R)-(4-Oxo-6-phenyl-hex-2-enyl)-5,6-dihydropyran-2-one (**1**): $[\alpha]_D^{20}$ = −61.2 (C 0.5, $CHCl_3$); IR ($CHCl_3$) ν = 3081, 1725, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.12 (m, 5H), 6.95–6.84 (m, 1H), 6.81 (dt, J = 15.1 Hz, 7.3 Hz, 1H), 6.24 (d, J = 14.9 Hz, 1 H), 6.01 (d, J = 9.1 Hz, 1H), 4.43 (m, 1H), 3.09–2.80 (m, 4H), 2.78–2.48 (m, 2H), 2.42–2.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 163.1, 144, 141.3, 140.3, 133.9, 129.1, 128.6, 126.5, 120.8, 75.4, 42.0, 36.9, 30.2, 283; MS (ESI): m/z = 293.1 (M^++Na).